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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/266,154	06/27/94	MORRISON S	RD1CIPFWCIII

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EXAMINER	
REEVES,J	

ART UNIT	PAPER NUMBER
1806	50

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/266,154	Applicant(s) Morrison et al
	Examiner Julie E. Reeves, Ph.D.	Group Art Unit 1806

☒ Responsive to communication(s) filed on *Sep 25, 1996*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *39-41, 43-48, 54, 55, 57, 58, 60-69, and 71-95* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *39-41, 43-48, 54, 55, 57, 58, 60-69, and 71-95* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Part III DETAILED ACTION

1. Claims 39-41, 43-48, 54-55, 57-58, 60-69 and 71-95 are pending before the Examiner.

2. Upon further consideration, for the reasons provided below concerning withdrawl the rejection set froth under 35 USC 103, the finality of the Office Action Paper no 41 filed 6/13/96) has been withdrawn. It is noted that the Appeal Brief (Paper no 48 filed 9/25/96) and request for a public hearing (Paper no 46 filed 6/17/96) have been filed and that the fees have been paid. Applicant may either ask for a refund of the Appeal fees or ask that these fees be put on credit towards a future appeal. The Examiner apologizes for the inconvenience.

Specification

3. The disclosure is objected to because of the following informalities: The Brief Description of the Drawings (page 2, lines 25-30) do not correctly label Figure 1A and Figure 1B as such. Amending line 25-30 to recite Figure 1A and Figure 1B in place of (a) and (b) would obviate this rejection. Appropriate correction is required. ok

Claim Rejections - 35 USC § 112

4. Claims 55, 66, 77 and 89 are rejected under 35 U.S.C. § 112, first and second paragraph, as the claimed invention is not described in such full, precise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The claims are indefinite for reciting "chimeric" as the exact meaning of the word is not known. The term chimeric is generic to a class of antibodies which are products drop-

of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies. The specification teaches inter and intra-species chimeras (see page 3) and teaches chimeras resulting from the fusion of variable and constant regions different types of receptors besides immunoglobulins. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

b. Moreover, the claims are vague and indefinite for reciting "substantially the same as" because it is unclear whether this claim encompasses point mutations, deletions, insertions or some other modifications of the variable and constant domains. Further, it is not clear what changes would be "substantially the same as": replacement with amino acids that have some of the same properties, for example a lysine replaced for an arginine, or perhaps replacing an arginine with a histidine? It is not clear whether the proposed substitutions encompass replacement or a negatively charged amino acid residue with a positively or uncharged amino acid residue. drop.

c. The specification does not enable chimeric antibodies commensurate in scope with the claims, as only chimeric antibodies having murine variable regions and human constant regions have been contemplated. drop. The technology required to produce CDR grafted chimeric antibodies was in its early stages of development and was highly unpredictable at the time applicant's invention was made. Modifications of the variable region which are involved in the production of CDR grafted chimeric antibodies often affect the specificity and affinity due to changes in the three dimensional conformation of the variable region. Loss of affinity is generally expected to adversely affect the therapeutic effectiveness of a monoclonal antibody. The specification provides no guidance or direction to one of ordinary skill in the art regarding how to produce CDR-grafted chimeric antibodies not other types of chimeric

antibodies. Furthermore, there is no guidance in the specification for the production of other types of fusion proteins which would fall in the category of "chimeric" antibody Undue experimentation would be required of one skilled in the art to produce mouse/human chimeric antibodies commensurate in scope with the claimed invention using the instant specification for guidance. Further to the above discussion, the specification provides no teaching or direction with respect to the myriad chimeric molecules in any particular application

d. Moreover, the specification does not enable variable domains which are "substantially the same as" as this reads upon various mutations, deletions, insertions and fusion proteins of the encoded protein. Since the specification has not identified which amino acid residues are critical or essential characteristics of the variable region, there is a lack of sufficient guidance to determine which amino acids substitutions or protein domain alterations could be made without altering the fundamental characteristics of the antibody and there are no working examples of any such variants. Since the state of the art of protein modification suggests that the effects of sequence alterations are unpredictable and since the specification provides no guidance as to which changes would result in an active antibody, undue experimentation would be required to determine which substitutions, deletions and insertions would encode an antigen binding antibody with all its identifying characteristics.

drop

5. Claims 47, 64, 75, 94 are rejected under 35 U.S.C. § 112, first and second paragraph, as the claimed invention is not described in such full, precise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear how an cell lines expressing a heavy chain can be concisidered an non-antibody producing cell as the heavy chain alone can bind antigen. If an antibody is defined by its ability to bind antigen, then the heavy chain alone would be considered an "antibody". The specification has notprovidede sufficient guidance and teachings to enable one skilled in the art to express of light and heavy chains in a cell line that already makes an immunoglobulin

heavy chain The specification has not provided a source for the cell lines that endogenously express a heavy chain and yet do not make a functional antibody. Limiting the claims to cells which endogenously produce a light chain would obviate this rejection.

6 Claims 39-41, 43-48, 54-55, 57-58, 60-69 and 71-95 are rejected and the specification is objected to under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure commensurate in scope with the claimed invention

a. Claims 39-41, 43-48, 54-55, 57-58, 60-69 and 71-77 recite the production of functional antibody by transfecting a non-antibody producing lymphoid cell. These claims encompass the transfection of other types of mammalian cells, including cells which do not normally produce antibody light and heavy chains, in addition to mammalian lymphoid cells

b. Clearly at the time of invention, one skilled in the art would know how to culture and transfect a variety of mammalian cells, including CHO hamster cells, HeLa human cells and CV-1 monkey cells. However, as evidenced by Falkner et al (Nature Vol 298 15 July 1982 286-288), Gillies et al (Nucleic acid Res Vol 11 No 22.7981-7997) and Stafford et al (Nature Vol 306:3 Nov 1983:77-79) transfecting the immunoglobulin genes into non-lymphoid cells presented a particular challenge at the time the claimed invention was made.

c In particular, Stafford et al (Nov 1983) showed that the rearranged immunoglobulin kappa light chain could be transfected into mouse myeloma cells but not detected when transfected into mouse 3T3 fibroblast or L cells. Stafford et al suggest that this result may be due to the failure of non-lymphoid cells to initiate transcription of the transfected immunoglobulin gene (see page 79 second to last paragraph).

d. Furthermore, Gillies et al (1983) demonstrate that functionally rearranged heavy and light chains introduced into mouse L tk- cells resulted in the low level expression of the Ig heavy chain however,the expression of the lambda or kappa light chains was not detected Gillies et al suggest that "the expression of the rearranged heavy and light chains are controlled differently and that these differences can be seen in transfected non-lymphoid cells" (see Abstract).

e. Further, Falkner et al (1982) teach that the transfection of the immunoglobulin kappa light chains in CV1 monkey cells and HeLa human cells was possible if the immunoglobulins were placed under the control of a simian virus promoter and that no significant expression of the kappa was detected under its own promoter (see Abstract). Falkner was not able to express the kappa chain in mouse L cells even with the simian promoter and the authors speculated that certain sequences from the kappa gene containing fragments may in some way interfere with the production of stable transcripts. Alternatively, something may be missing from our systems" (page 288, last full paragraph). It is noted that the viral promoter which aided the Ig light chain expression in CV-1 cells but did not overcome the expression problems Falkner encountered with the L cells.

f. Moreover, the specification does not provide adequate teachings to overcome the deficiencies set forth in the art so that one skilled in the art would know how toexpress Ig heavy and light chains in any mammalian cell line. The specification merely teaches that "[i]n order for the expression of the fused gene, it will be necessary to have transcriptional and translational signals recognized by an appropriate eukaryotic host. For the most part, desirable eukaryotic hosts will be mammalian cells capable of culture in vitro, particularly leukocytes, more particularly myeloma cells or other transformed or oncogenic lymphocyte..." (page 8, last paragraph). The specification does not teach what these transcriptional and translational signals may be or which sigtnals would be necessary for which types of mammalian cells The specification provides no suggestion or guidance to use a viral

promoter, such as the simian virus SV40 promoter found by Falkner to be a necessary requirement for the expression the kappa chain in CV1 cells A viral promoter is not encompassed by the term "eukaryotic promoter" as a virus do not belong to the class of eukaryotic cells as it lacks a nucleus. It is further noted that Falkner's viral promoter aided the expression of Ig chains in CV-1 cells but did not overcome Falkner's L cell expression problems. Similarly, Stafford could not express the rearranged light chain in 3T3 cells or L cells. Gillies was able to detect heavy chain expression but not light chain expression in L cells. These negative and conflicting results demonstrate that the field of expressing immunoglobulin genes into non-lymphoid mammalian cells was unpredictable at the time the application was filed and, considereing the lack of teachings in the specification, one skilled in the art would not know how to transfect non-lymphoid mammalian cells with immunoglobulin genes without undue experimentation. Amending the claims to recite "mammalian lymphoid cells" would obviate this rejection.

g. The 1.132 Declaration of Sherie L. Morrison dated 18 August 1993, Paper no 30 filed 9/24/96 states that there was no reason to believe that the J558L cell line differed from other mammalian cells with respect to its ability to express its endogenous genes and because mammalian cells were known to express assemble and secrete large quantities of antibody protein encoded by endogenous genes (see page 5, paragraph 12). This is not convincing because the arguments presented are not commensurate in scope with the claimed invention. The references cited to support the assertion that mammalian cells are known to produce antibodies (Scharff et al, Exhibits B and C) both concern the expression of immunoglobulin genes in myeloma cells. The endogenous expression of immunoglobulin genes, either in myeloma cells or other lymphocytes is enabled by the teachings in the specification. However, as evidenced by Falkner et al, Gillies et al, and Stafford et al, which establish the unpredictable nature of expressing Immunoglobulin genes in non-lymphocytes, expression of immunoglobulin genes in non-lymphocytes posed problems at the time the claiemd invention was made.

h Claims 78-95 recite the production of functional antibody by transfecting a non-antibody producing lymphoid cell. These claims encompass the transfection of non-mammalian cells, including the transfection of avian, fish, reptilian and amphibian lymphoid cells. moreover, the specification taches that the term non-mammalian encompasses fungi, yeast, filamentous fungi or the like" (page 8, last paragraph). At the time the claimed invention was made, the isolation and culturing of cell lines from creatures other than mammals was in its early stages. The isolation of lymphoid cells from non-mammalian species was unpredictable at the time the application was filed and the successful transfection of antibody light and heavy chains into non-mammalian lymphoid cells has not been enabled by the teachings in the specification. Nor was the transfection of antibody heavy and light chain genes into non-mammalian lymphoid cells routinely practiced in the art at the time the invention was filed. Amending the claims to recite "mammalian lymphoid cells" would obviate this rejection Please note that upon amendment, claims 78-95 will be duplicative of the amended Claims 39-41, 43-48, 54-55, 57-58, 60-69 and 71-77.

Claim Rejections - 35 USC § 103

7. The rejection of Claims 39-41, 43-48, 54-55, 57-58, 60-69 and 71-95 set forth under 35 USC § 103 as being unpatentable over Cabilly (L, R, or 2A) in view of Gillies (Cell 1983) has been withdrawn upon further consideration. Applicant's Appeal Brief filed 30 Sept 1996 is persuasive regarding the fact that Cabilly et al does not disclose the production of functional antibodies (see pages 8-12). The Appeal Brief is also persuasive regarding the fact that the Gillies article does not describe the production of functional antibodies, but rather the expression of a heavy chain specific for one epitope in a cell line that consitutively produced a light chain specific for a second, different epitope. Applicant is correct in arguing that even if Gillies had demonstrated the correct assembly of the transfected in heavy and the endogenously expressed light chain, a result which Gillies did not demonstrate, this combination of heavy and light chains could not form a functional, antigen binding

antibody Accordingly, the claims are deemed to be free of the prior art. Upon filing the amendments to the claims suggested in this Office Action, the claims would be considered in condition for allowance.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Reeves, Ph.D., whose telephone number is (703) 308-7553 The examiner can normally be reached on Monday through Friday from 9:00 am to 5.30 pm If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

9. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1806 via the fax phone number (703) 305-7939. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Respectively,

Julie Reeves

Julie E. Reeves, Ph.D.

(703) 308-7553

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800